Clinical Spectrum of Holoprosencephaly: A Clinical-Neuroradiologic Analysis of the Experience at the Carter Centers for Research in Holoprosencephaly and Related Brain Malformations.

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Background: Holoprosencephaly (HPE) is a brain malformation which results from incomplete cleavage of the prosencephalon into the left and right hemispheres. HPE has been classified into 3 types: alobar, semilobar, and lobar. Children with HPE have numerous neurological problems including mental retardation, cerebral palsy, seizure disorder, and endocrinologic problems.(1) *Objective:* To better characterize the clinical characteristics of patients with HPE and to correlate neuroimaging findings with specific clinical characteristics. *Methods:* We evaluated 68 children with HPE at one of three Carter Centers. The diagnosis was confirmed on neuroimaging studies (MRI or high-quality CT). Evaluations included a comprehensive history, developmental assessment, and physical examination. Specific characteristics of the patients were assessed including 7 clinical, 3 developmental, and 4 motor variable. Neuroimaging studies were assessed by 2 pediatric neuroradiologists who assessed the type of HPE, and also graded the degree of non-separation of the deep gray nuclei.(2) They also noted the presence or absence of dorsal cyst and cortical malformation.(3, 4) *Results:* Seizures occurred in approximately half of the children with HPE. The presence of cortical malformation was associated with seizures that were difficult to control. Endocrinologic dysfunction was noted in 72% of the patients with all having at least diabetes insipidus. The severity of endocrine abnormality correlated with the degree of hypothalamic non-separation ($p=0.029$). Temperature regulation problem, seen in 32%, was also associated with the degree of hypothalamic non-separation ($p=0.0013$). There was a correlation between the severity of the facial malformation and the severity of and the severity of the HPE type ($p = 0.032$). However, there were many exceptions. Microcephaly was noted in 73%. Among motor abnormalities, dystonia was correlated with the degree on non-separation of the caudate and lentiform nuclei, as well as, the grade of HPE. Hypotonia was correlated with the grade of HPE. Mobility, upper extremity function, and language were all significantly correlated with the degree of non-separation of the caudate, lentiform, and thalamic nuclei and grade of HPE. In addition, there was a good correlation between the Composite Fusion Score (sum of the grades of deep nuclei non-separation) and the Composite Severity Score (sum of grades of clinical and developmental variables excluding facial malformations). *Conclusions:* Holoprosencephaly represents a spectrum of malformations resulting from a failure of complete separation of the structures of the forebrain. This is the first prospective study that examines the correlation of clinical and neuroradiologic characteristics of patients with HPE. In general, the severity of clinical and neurological problems parallels the severity of the HPE type. These problems also correlate with the degree of non-separation of the deep gray nuclei. This suggests that the embryologic defects in the ventral patterning that result in HPE involve the separation of the hemispheres and deep midline structures.(5) By combining the detailed neuroradiologic features of HPE with systematic clinical assessments, we have developed a more accurate classification scheme for predicting neurodevelopmental outcome and potential clinical problems.

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